

# Use of Tetracycline With Amphotericin B for Gonorrhea in Males

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GONORRHEA is still a major public health problem, despite the development of sulfonamides (1) and of penicillin (2,3). The appearance and wide dissemination of sulfonamide-resistant strains of gonococci during and shortly after the Second World War might well have reduced the physician to his former helplessness in the face of this disease had not penicillin become available during that period. There are, however, important limitations to the usefulness of penicillin. Not only have penicillin-resistant strains of gonococci appeared (4,5), but many patients are sensitive to this antibiotic (5,6).

Fortunately, tetracycline is effective against gonococcal infection and already is widely used in the treatment of penicillin-sensitive patients (7). The use of broad-spectrum antibiotics can, however, disturb the internal ecology by permitting the overgrowth of nonsensitive organisms, including the yeastlike forms, such as *Candida albicans* (7-10). Therefore, it may be advisable to administer an antifungal agent prophylactically when a broad-spectrum antibiotic is given, especially if the antibiotic is administered in high dosage. It has been remarked, however, that the addition of such an agent adds nothing to the therapeutic effectiveness of tetracycline and introduces the possibilities of development of antibiotic-resistant strains of fungi and the further enhancement of overgrowth of potentially dangerous organisms.

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An orally administered formulation combining tetracycline and amphotericin B was used as the original treatment in a large number of patients with acute gonococcal urethritis seen in the principal venereal disease clinic in Philadelphia, Pa.

During a period of 4 months, all male patients, aged 18 years and over, admitted to the clinic were offered a choice of the conventional intramuscular treatment with penicillin or a combined oral formulation of tetracycline and amphotericin B for their acute gonorrheal infections. Those who chose the oral therapy were screened for their caseholding potential by the full-time public health nurse assigned to the study. Of these patients, 234, 9 white and 225 nonwhite, were accepted for the study. However, in pretreatment diagnosis, 22 patients had negative cultures or smears. Each of the remaining 212 patients consumed in the presence of the nurse eight capsules constituting a single oral dose of 2 grams tetracycline, and each patient was instructed to return to the clinic for 3 consecutive weeks for post-treatment observation. One hundred patients returned to the clinic for 3 weeks, 50 for 2 weeks, 41 for 1 week, and 21 patients were lost to followup.

The sole medication used was a combined formulation of phosphate potentiated tetracycline and the antimycotic agent amphotericin B. Dosage was determined by the tetracycline content of the medication. The modality used was a capsule containing tetracycline phosphate complex equivalent to 250 mg. tetracycline hydrochloride and 50 mg. amphotericin B. Eight such capsules constituted the single oral dose of 2 gm. tetracycline given to each patient.

Detailed laboratory studies, performed for

diagnostic purposes at the initial visit, on 97 patients consisted of direct smear of exudate for gram stain, direct fluorescent antibody (FA) smear, FA delayed culture (11-14), and conventional culture (table 1). It became apparent that the gram-stained smear was equal for all practical purposes to any combination of the above procedures for diagnosis, and that the number of possible false positive smears would be quite small. In the remaining patients, therefore, this alone was performed.

Laboratory evaluation of cure following treatment was obtained by study of urine sediment at each post-treatment visit. These studies included FA direct smear, FA delayed culture, and conventional culture. Conventional cultures included sugar fermentation studies of each isolated suspected organism. Urinary sediment was obtained by collecting the first 200 ml. of a freshly voided specimen, from which a sample of 20 ml. was taken. This sample was centrifuged, decanted, and the remaining sediment used as the source of material for study. The results obtained from 384 urine specimens are shown in table 2.

Of the 191 patients for whom followup was possible, there was initial cure for 180, a recovery rate of 94 percent. While it is possible that most of the 21 patients who did not return for observation were also cured (uncured patients usually return for further treatment), this cannot be stated with certainty.

Cure is defined as the absence of clinical and laboratory evidence of gonorrhea on at least one occasion during the post-treatment observation period; reinfection is defined as the reappear-

**Table 1. Results of urethral discharge studies on 97 patients with gonorrhea, at initial visit to clinic**

Number of patients	Routine smear	FA smear	FA culture	Routine culture
57-----	+	+	+	+
7-----	-	-	-	-
11-----	+	-	+	+
6-----	+	+	+	-
9-----	+	+	-	+
2-----	+	+	-	-
1-----	-	-	+	+
2-----	-	+	+	-
2-----	+	-	-	+

NOTE: FA—fluorescent antibody.

**Table 2. Results of urine sediment studies for gonococcal infection, using 384 specimens**

Number of specimens	FA smear	FA culture	Routine culture
4-----	+	+	+
345-----	-	-	-
9-----	-	+	+
11-----	-	-	+
11-----	-	+	-
1-----	+	-	-
3-----	+	+	-

NOTE: FA—fluorescent antibody.

ance of gonorrheal symptoms, and their confirmation by laboratory tests, after an initial cure has been established. By these criteria, 11 of the patients classified as cured became reinfected before the end of the observation period. Seven of these individuals admitted reexposure.

The oral administration of tetracycline with amphotericin B, even at the large dosage used, produced no serious systemic effects. Four patients complained of transitory nausea, and in one there was some emesis. The reaction rate was thus only 1.4 percent. No secondary infections by *Monilia* or other yeastlike organisms occurred. It was thus our experience that tetracycline with amphotericin B, administered orally, appeared to be an effective and safe medication for the treatment of acute gonococcal urethritis in the male, particularly in patients with a history of sensitivity to penicillin.

We agree with Taubenhaus (15) that research should be an organized, planned, and continuing activity of a health department. This would seem to be particularly so with regard to venereal disease, where large city clinics may be the only source of sufficiently large numbers of patients to readily conduct clinical studies. In this study, in a relatively short period of 4 months, approximately 200 suitable patients were available, and we were able to follow about 90 percent for a period long enough to include them in the study.

Considering the characteristics of the treated asymptomatic males in this series, the 90 percent caseholding rate is quite commendable, and it points up the desirability, in planning original clinical research programs, of assigning a qualified individual to be solely responsible for keeping patients on post-treatment observation.

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## Placebo Therapy

At the time we were conducting the study on the efficacy of tetracycline with amphotericin B for gonorrhea in males at Philadelphia's principal venereal disease clinic, statements were made that placebo "therapy" cured a sizable number of such patients. If this were indeed true, it would tend to negate even the most carefully controlled research. Therefore, we decided to test, in an unbiased fashion, the validity of these statements.

Twenty-five symptomatic males were chosen at random from the venereal disease clinic population by the public health nurse assigned to the tetracycline study. Each of the patients, in the presence of the nurse, consumed four placebo capsules identical in appearance to the tetracycline capsules. The patients were instructed to return promptly if their subjective symptoms did not disappear in 48 hours or longer, or if such symptoms returned after initial disappearance.

Laboratory tests consisted of a smear of the urethral discharge for gram staining on initial visit, and on subsequent visits, study of urinary sediment by the FA direct smear, FA delayed culture, and routine culture. Routine cultures always included sugar fermentation studies of suspected organisms.

Six of the 25 patients were excluded from the study: 2 failed to return to the clinic, and 4 patients' laboratory tests were negative for gonorrhea. The remaining 19 patients had positive smears.

On a return visit, in 1 week or less, three patients stated that their subjective symptoms were improved. However, sugar fermentation studies proved their urine still contained culturable gonococcal organisms. The other 16 patients indicated no subjective improvement, and for 13 of these patients living gonococci were demonstrated in the urine sediment. Urinary sediment studies were not performed for three patients.

A 24-year-old Negro male apparently became an asymptomatic carrier of gonococci. A brief summary of his experience follows:

On October 4, 1961, the patient had a purulent urethral discharge in which gram-negative

intracellular organisms were seen on the gram smear. He was given placebo therapy. On October 11, the patient stated that his symptoms had cleared gradually in 4 days, and he was found subjectively and objectively asymptomatic. However, at this time, gonococci in his urine sediment were revealed by FA technique and routine culture. When seen on October 18, the patient said his only symptom was an occasional small amount of discharge when washing. Again, the FA delayed and routine cultures were positive. On October 25 he was asymptomatic and objectively well. On this visit the FA direct smear was positive, the FA delayed culture was negative, and the routine culture was unsatisfactory. Although the patient was still asymptomatic on November 1, the FA delayed and routine cultures were again positive, and he received 2 grams of tetracycline phosphate with amphotericin B in the presence of the nurse. On November 8, 15, and 22, the patient was asymptomatic, and all laboratory studies of urinary sediment were negative.

Each of the remaining 18 patients was given eight capsules (250 mg. each) of tetracycline with amphotericin B on his first return visit after receiving placebo "treatment." Seventeen patients were subjectively and objectively cured in 1 week or slightly longer after therapy, and their laboratory tests were negative. One patient's urine sediment contained living gonococci 2 weeks after he received tetracycline, and he was re-treated with 2.4 million units of benzathine penicillin G. This was a case of reinfection or treatment failure.

In summation, it would seem that laboratory-confirmed gonococcal infection in males is not cured by placebo "therapy" even though in one instance subjective complaints disappeared.

This study demonstrated the possibility that a male with acute gonorrheal urethritis may, in the absence of therapy, have a spontaneous remission of symptoms and become an asymptomatic carrier of gonorrhea.

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In this study a public health nurse was assigned full time to the project. She interviewed and screened each patient on the initial visit, kept records, administered all medication, gave return appointments, and saw each patient at every clinic visit. Delinquent patients were followed by personally written post cards, telephone calls, and when needed, home visits.

Laboratory results confirmed the generally accepted opinion that the gram-stained smear, because of its simplicity and accuracy, is the procedure of choice for the diagnosis of male gonorrhoeal urethritis. The more complicated FA techniques did not seem to offer any additional advantage.

In the post-treatment study of urine sediment, the FA delayed culture was the most sensitive procedure of testing urinary sediment. However, the combination of FA culture and routine culture yielded the highest number of positive results.

In this study two patients were found to be asymptomatic carriers of gonococci following apparent cure of their acute gonorrhoeal urethritis. A brief résumé of these two cases follows:

*Case 1.* A 21-year-old male, seen on April 7, 1961, had a urethral discharge and laboratory-confirmed gonorrhoea. He was treated on the same day, and the discharge cleared in 48 hours. On April 14, the patient was clinically well, the FA smear of the urine sediment was negative, and the FA culture and the routine culture of the sediment were positive. On April 21 he was clinically well, and all laboratory tests were negative. However, on April 28 and on three more consecutive weekly examinations, although the patient remained asymptomatic, gonococci were cultured from his urine sediment by routine and FA culture methods. He was re-treated on June 15. On June 22 and 29 the urine sediment tests were negative except for one positive FA smear obtained on June 29.

*Case 2.* A 27-year-old male with urethral discharge and a positive smear for gonococci was seen on May 24, 1961. He was treated the same day, and the discharge cleared in 48 hours. On June 8 the patient was clinically well, the FA smear and culture of the urine sediment were negative, but the routine conventional culture was positive. On June 15 and 22 the patient was asymptomatic, but all laboratory tests on

the urine were positive. The FA culture was also positive on July 5, but the routine culture was negative, and the patient was re-treated the same day. He was last seen on July 26, at which time he was clinically well and all laboratory tests were negative.

Both of these patients, on repeated occasions following clinical cure of their acute gonorrhoeal urethritis, had live gonococci in their urine, although they had no symptoms or objective clinical evidence of infection. The organisms isolated fulfilled all cultural criteria for gonococci, including characteristic sugar fermentations and staining with specific fluorescent-labeled antiserum by FA techniques. Whether these organisms were present as a result of the original treated infection or a subsequent asymptomatic reinfection cannot be determined, although the former possibility seems more likely.

The asymptomatic male carrier of living gonococci seems to exist as a companion to the well-known asymptomatic female carrier. His prevalence and importance in the control of gonorrhoea is not established but should warrant notice and further study.

We feel that this study points up the importance of evaluating a new technique (FA methods) against well-established ones (the gram smear and conventional culture), the efficiency of which in the study of male gonorrhoea is accurately known.

## Summary

In 4 months a combined formulation of phosphate potentiated tetracycline and the antifungal antibiotic amphotericin B was administered orally to 212 male patients with acute gonococcal urethritis who were seen at a venereal disease clinic in Philadelphia, Pa.

Of the 191 patients for whom followup was possible, 180, or 94 percent, appeared to be cured with the initial treatment. Eleven of these cured patients became reinfected before the end of the study. Tetracycline with amphotericin B, administered orally, seemed to be safe and effective for the study patients. There were no allergic reactions, and the only side effect was transient nausea in four patients, with emesis in one.

In a comparison of two new procedures, the direct and delayed fluorescent antibody tests, with the routine smear and culture techniques for the study of gonococcal infection in the male, the routine smear was the most practical method for diagnosis, whereas a combination of the fluorescent antibody delayed culture and routine culture yielded the most positive results in post-treatment study of urine sediment.

Two patients were found to be asymptomatic carriers of gonococci after they were apparently cured of gonorrhoeal urethritis.

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## Papers on Medical Care

Papers presented at the general sessions of the annual meeting of the Southern Branch, American Public Health Association, Roanoke, Va., May 2-4, 1962, have been reproduced for sale to interested persons.

The theme of the meeting, "Medical Care—Its Place in Public Health," was discussed by 13 speakers representing the American Dental Association, the American Hospital Association, the American Medical Association, the American Nurses' Association, Federal and local health agencies, and voluntary organizations.

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